## 1.9 Product Information

### 1.9.1. Summary of Product Characteristics

Summary of Product Characteristics is enclosed overleaf.

**SUMMARY OF PRODUCT CHARACTERISTICS**

# PACSITA

## Capecitabine Tablets USP 150 mg and 500 mg

*Rx Only*

**NAME OF THE PRODUCT** : Capecitabine Tablets USP 150 mg
Capecitabine Tablets USP 500 mg

**(TRADE) NAME OF PRODUCT** : **PACSITA 150**
**PACSITA 500**

**STRENGTH** : 150 mg and 500 mg

**PHAPMACEUTICAL DOSAGE FORM**: Tablet

**QUALITATIVE AND QUANTITATIVE COMPOSITIONS**:

*Capecitabine Tablets USP 150 mg*

Each film-coated tablet contains 150 mg of capecitabine USP

*Capecitabine Tablets USP 500 mg*

Each film-coated tablet contains 500 mg of capecitabine USP

**PHARMACEUTICAL FORM**

*Capecitabine Tablets USP 150 mg*

Light peach colored biconvex, oblong shaped film coated tablets, debossed with 150 on the one side and plain on the other side.

*Capecitabine Tablets USP 500 mg*

Peach colored biconvex, oblong shaped film coated tablets, debossed with 500 on the one side and plain on the other side.

**CLINICAL PARTICULARS**

**Therapeutic indications**

Capecitabine Tablets is indicated for the treatment of:
-for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.

- metastatic colorectal cancer.
- first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.
- in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.
- as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

**Posology and method of administration**

Capecitabine Tablets should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic medicinal products. Careful monitoring during the first cycle of treatment is recommended for all patients.
Treatment should be discontinued if progressive disease or intolerable toxicity is observed. Standard and reduced dose calculations according to body surface area for starting doses of Capecitabine Tablets of 1250 mg/m$^2$ and 1000 mg/m$^2$ are provided in tables 1 and 2, respectively.

Posology
Recommended posology:

*Monotherapy*

*Colon, colorectal and breast cancer*
Given as monotherapy, the recommended starting dose for capecitabine in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m$^2$ administered twice daily (morning and evening; equivalent to 2500 mg/m$^2$ total daily dose) for 14 days followed by a 7-day rest period.
Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

*Combination therapy*
*Colon, colorectal and gastric cancer*
In combination treatment, the recommended starting dose of capecitabine should be reduced to 800 - 1000 mg/m$^2$ when administered twice daily for 14 days followed by a 7-day rest period, or to 625 mg/m$^2$ twice daily when administered continuously. For combination with irinotecan, the recommended starting dose is 800 mg/m$^2$ when administered twice daily for 14 days followed by a 7-day rest period combined with irinotecan 200 mg/m$^2$ on day 1. The inclusion of bevacizumab in a combination regimen has no effect on the starting dose of capecitabine. Premedication to maintain adequate hydration and anti-emesis according to the cisplatin summary of product characteristics should be started prior to cisplatin administration for patients receiving the capecitabine plus cisplatin combination. Premedication with antiemetics according to the oxaliplatin summary of product characteristics is recommended for patients receiving the capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a duration of 6 months.

*Breast cancer*

In combination with docetaxel, the recommended starting dose of capecitabine in the treatment of metastatic breast cancer is 1250 mg/m$^2$ twice daily for 14 days followed by a 7- day rest period, combined with docetaxel at 75 mg/m$^2$ as a 1 hour intravenous infusion every 3 weeks. Premedication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the capecitabine plus docetaxel combination.

*Capecitabine dose calculations*

Table 1 Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1250 mg/m$^2$

| Dose level 1250 mg/m$^2$ (twice daily) | | | | | |
|---|---|---|---|---|---|
| Body Surface Area (m$^2$) | Full dose 1250 mg/m$^2$ | Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening) | | Reduced dose (75%) 950 mg/m$^2$ | Reduced dose (50%) 625 mg/m$^2$ |
| | Dose per administration (mg) | 150 mg | 500 mg | Dose per administration (mg) | Dose per administration (mg) |
| ≤1.26 | 1500 | - | 3 | 1150 | 800 |
| 1.27 - 1.38 | 1650 | 1 | 3 | 1300 | 800 |
| 1.39 - 1.52 | 1800 | 2 | 3 | 1450 | 950 |
| 1.53 - 1.66 | 2000 | - | 4 | 1500 | 1000 |
| 1.67 - 1.78 | 2150 | 1 | 4 | 1650 | 1000 |
| 1.79 - 1.92 | 2300 | 2 | 4 | 1800 | 1150 |
| 1.93 - 2.06 | 2500 | - | 5 | 1950 | 1300 |
| 2.07 - 2.18 | 2650 | 1 | 5 | 2000 | 1300 |
| ≥2.19 | 2800 | 2 | 5 | 2150 | 1450 |

Table 2 Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1000 mg/m$^2$

| Dose level 1000 mg/m$^2$ (twice daily) | | | | | |
|---|---|---|---|---|---|
| Body Surface Area (m$^2$) | Full dose 1000 mg/m$^2$ | Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening) | | Reduced dose (75%) 750 mg/m$^2$ | Reduced dose (50%) 500 mg/m$^2$ |
| | Dose per administration (mg) | 150 mg | 500 mg | Dose per administration (mg) | Dose per administration (mg) |
| ≤1.26 | 1150 | 1 | 2 | 800 | 600 |
| 1.27 - 1.38 | 1300 | 2 | 2 | 1000 | 600 |
| 1.39 - 1.52 | 1450 | 3 | 2 | 1100 | 750 |
| 1.53 - 1.66 | 1600 | 4 | 2 | 1200 | 800 |
| 1.67 - 1.78 | 1750 | 5 | 2 | 1300 | 800 |
| 1.79 - 1.92 | 1800 | 2 | 3 | 1400 | 900 |
| 1.93 - 2.06 | 2000 | - | 4 | 1500 | 1000 |
| 2.07 - 2.18 | 2150 | 1 | 4 | 1600 | 1050 |
| ≥2.19 | 2300 | 2 | 4 | 1750 | 1100 |

*Posology adjustments during treatment*

*General*

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time.

For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption.

Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced. The following are the recommended dose modifications for toxicity:

Table 3 Capecitabine dose reduction schedule (3 weekly cycle or continuous treatment)

| Toxicity grades* | Dose changes within a treatment cycle | Dose adjustment for next cycle/dose (% of starting dose) |
|---|---|---|
| • *Grade 1* | Maintain dose level | Maintain dose level |
| • *Grade 2* | | |
| -1st appearance | Interrupt until resolved to grade 0-1 | 100% |
| -2nd appearance | | 75% |
| -3rd appearance | | 50% |
| -4th appearance | Discontinue treatment permanently | Not applicable |
| • *Grade 3* | | |
| -1st appearance | Interrupt until resolved to grade 0-1 | 75% |
| -2nd appearance | | 50% |
| -3rd appearance | Discontinue treatment permanently | Not applicable |
| • *Grade 4* | | |
| -1st appearance | Discontinue permanently *Or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1 | 50% |
| -2nd appearance | Discontinue permanently | Not applicable |

*According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 4.0.

*Haematology*

Patients with baseline neutrophil counts of $<1.5 \times 10^9$/L and/or thrombocyte counts of $<100 \times 10^9$/L should not be treated with capecitabine. If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below $1.0 \times 10^9$/L or that the platelet count drops below $75 \times 10^9$/L, treatment with capecitabine should be interrupted.

*Dose modifications for toxicity when capecitabine is used as a 3 weekly cycle in combination with other medicinal products*

Dose modifications for toxicity when capecitabine is used as a 3 weekly cycle in combination with other medicinal products should be made according to table 3 above for capecitabine and according to the appropriate summary of product characteristics for the other medicinal product(s).

At the beginning of a treatment cycle, if a treatment delay is indicated for either capecitabine or the other medicinal product(s), then administration of all therapy should be delayed until the requirements for restarting all medicinal products are met.

During a treatment cycle for those toxicities considered by the treating physician not to be related to capecitabine, capecitabine should be continued and the dose of the other medicinal product should be adjusted according to the appropriate Prescribing Information.

If the other medicinal product(s) have to be discontinued permanently, capecitabine treatment can be resumed when the requirements for restarting capecitabine are met.

This advice is applicable to all indications and to all special populations.

*Dose modifications for toxicity when capecitabine is used continuously in combination with other medicinal products*

Dose modifications for toxicity when capecitabine is used continuously in combination with other medicinal products should be made according to table 3 above for capecitabine and according to the appropriate summary of product characteristics for the other medicinal product(s).

*Posology adjustments for special populations:*

*Hepatic impairment*

No information is available on hepatic impairment due to cirrhosis or hepatitis.

*Renal impairment*

Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min [Cockcroft and Gault] at baseline). The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 ml/min at baseline) may be increased compared to the overall population. In patients with moderate renal impairment at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m$^2$ is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1000 mg/m$^2$. In patients with mild renal impairment (creatinine clearance 51-80 ml/min at baseline) no adjustment of the starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3 or 4 adverse event during treatment and subsequent dose adjustment as outlined in table 3 above. If the calculated creatinine clearance decreases during treatment to a value below 30 ml/min, Capecitabine tablets should be discontinued. These dose adjustment recommendations for renal impairment apply both to monotherapy and combination use (see also section “Elderly” below).

*Elderly*
During capecitabine monotherapy, no adjustment of the starting dose is needed. However, grade 3 or 4 treatment-related adverse reactions may be more frequent in patients ≥60 years of age compared to younger patients.
When capecitabine was used in combination with other medicinal products, elderly patients (≥65 years) may experience more grade 3 and grade 4 adverse drug reactions, including those leading to discontinuation, compared to younger patients. Careful monitoring of patients ≥60 years of age is advisable.
- *In combination with docetaxel*: an increased incidence of grade 3 or 4 treatment-related adverse reactions and treatment-related serious adverse reactions may be observed in patients 60 years of age or more. For patients 60 years of age or more, a starting dose reduction of capecitabine to 75% (950 mg/m$^2$ twice daily) is recommended. If no toxicity is observed in patients ≥60 years of age treated with a reduced capecitabine starting dose in combination with docetaxel, the dose of capecitabine may be cautiously escalated to 1250 mg/m$^2$ twice daily.
*Paediatric population*
There is no relevant use of capecitabine in the paediatric population in the indications colon, colorectal, gastric and breast cancer.

Method of administration
Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

**Contraindications**

- History of severe and unexpected reactions to fluoropyrimidine therapy,
- Hypersensitivity to capecitabine or to any of the excipients used in manufacturing of capecitabine tablets or fluorouracil,
- In patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity,
- During pregnancy and lactation,
- In patients with severe leukopenia, neutropenia, or thrombocytopenia,
- In patients with severe hepatic impairment,
- In patients with severe renal impairment (creatinine clearance below 30 ml/min),
- Treatment with sorivudine or its chemically related analogues, such as brivudine,
- If contraindications exist to any of the medicinal products in the combination regimen, that medicinal product should not be used.

**Special warnings and precautions for use**

Dose limiting toxicities
Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia). Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.

*Diarrhoea*. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) may be used. NCIC CTC grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption. Grade 4 diarrhoea is an increase of ≥10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Dose reduction should be applied as necessary.

*Dehydration.* Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxicmedicinal products. Acute renal failure secondary to dehydration might be potentially fatal. If grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected.
Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be applied for the precipitating adverse event as necessary.

*Hand-foot syndrome* (also known as hand-foot skin reaction or palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema). Grade 1 hand-foot syndrome is defined as numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities.
Grade 2 hand-foot syndrome is painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints which could impact patient identification. If grade 2 or 3 hand-foot syndrome occurs, administration of Capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased. When capecitabine and cisplatin are used in combination, the use of vitamin B6 (pyridoxine) is not advised for symptomatic or secondary prophylactic treatment of hand–foot syndrome, because of published reports that it may decrease the efficacy of cisplatin. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with Capecitabine Tablets.

*Cardiotoxicity.* Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse reactions may be more common in patients with a prior history of coronary artery disease.
Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy may be reported in

patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris.

*Hypo- or hypercalcaemia.* Hypo- or hypercalcaemia may be reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia.

*Central or peripheral nervous system disease.* Caution must be exercised in patients with central or peripheral nervous system disease, e.g. brain metastasis or neuropathy.

*Diabetes mellitus or electrolyte disturbances.* Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.

*Coumarin-derivative anticoagulation.* Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly.

*Hepatic impairment.* Capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur. Treatment with capecitabine monotherapy may be resumed when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

*Renal impairment.* The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) may be increased compared to the overall population.

*Dihydropyrimidine dehydrogenase (DPD) deficiency*: Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU may be attributed to a deficiency of DPD activity.
Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Although DPD deficiency cannot be precisely defined, it is known that patients with certain homozygous or certain compound heterozygous mutations in the *DPYD* gene locus (e.g. DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants), which can cause complete or near complete absence of DPD enzymatic activity (as determined from laboratory assays), have the highest risk of life-threatening or fatal toxicity and should not be treated with capecitabine. No dose has been proven safe for patients with complete absence of DPD activity.
Patients with certain heterozygous DPYD variants (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) may have increased risk of severe toxicity when treated with capecitabine.

For patients with partial DPD deficiency (such as those with heterozygous mutations in the *DPYD* gene) and where the benefits of capecitabine are considered to outweigh the risks (taking into account the suitability of an alternative nonfluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution and frequent monitoring with dose adjusment according to toxicity. A reduction of the starting dose in these patients may be considered to avoid serious toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by specific test. The DPYD*2A, c.1679T>G variants lead to a greater reduction in enzymatic activity than the other variants with a higher risk of side effects. The consequences of a reduced dose for efficacy are currently uncertain. Therefore, in the absence of serious toxicity the dose could be increased while carefully monitoring the patient.

The patients who are tested negative for the above-mentioned alleles may still have a risk of severe adverse events.

In patients with unrecognised DPD deficiency treated with capecitabine as well as in those patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur. In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

*Ophthalmologic complications:* Patients should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate.

*Severe skin reactions:* Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Capecitabine should be permanently discontinued in patients who experience a severe skin reaction during treatment.
As this medicinal product contains anhydrous lactose as an excipient, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Interaction with other medicinal products and other forms of interaction**
Interaction studies have only been performed in adults.

Interaction with other medicinal products
*Cytochrome P-450 2C9 substrates:* Care should be exercised when capecitabine is co-administered with 2C9 substrates (e.g., phenytoin)

*Coumarin-derivative anticoagulants:* altered coagulation parameters and/or bleeding may be reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These reactions may occur within several days and up to

several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly.

*Phenytoin:* increased phenytoin plasma concentrations resulting in symptoms of phenytoin intoxication in single cases may be reported during concomitant use of capecitabine with phenytoin. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

*Folinic acid/folic acid*: Folinic acid has no major effect on the pharmacokinetics of capecitabine and its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine and its toxicity may be enhanced by folinic acid: the maximum tolerated dose (MTD) of capecitabine alone using the intermittent regimen is 3000 mg/m$^2$ per day whereas it is only 2000 mg/m$^2$ per day when capecitabine was combined with folinic acid (30 mg orally bid). The enhanced toxicity may be relevant when switching from 5- FU/LV to a capecitabine regimen. This may also be relevant with folic acid supplementation for folate deficiency due to the similarity between folinic acid and folic acid.

*Sorivudine and analogues:* The interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.

*Antacid:* There may be a small increase in plasma concentrations of capecitabine and one metabolite (5'-DFCR); there was no effect on the 3 major metabolites (5'-DFUR, 5-FU and FBAL) when administered with aluminium hydroxide and magnesium hydroxide-containing antacid.

*Allopurinol:* interactions with allopurinol may be observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

*Interferon alpha:* the MTD of capecitabine was 2000 mg/m$^2$ per day when combined with interferon alpha-2a (3 MIU/m$^2$ per day) compared to 3000 mg/m$^2$ per day when capecitabine was used alone.

*Radiotherapy:* the MTD of capecitabine alone using the intermittent regimen is 3000 mg/m$^2$ per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of capecitabine is 2000 mg/m$^2$ per day using either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

*Oxaliplatin*: no clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occurred when capecitabine was administered in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab.

*Bevacizumab*: there was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites in the presence of oxaliplatin.

*Food interaction*
It is recommended that capecitabine should be administered with food. Administration with food decreases the rate of capecitabine absorption.

**Fertility, pregnancy and lactation**
Women of childbearing potential/Contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine. If the patient becomes pregnant while receiving capecitabine, the potential hazard to the foetus must be explained. An effective method of contraception should be used during treatment.

Pregnancy
It should be assumed that capecitabine may cause foetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. Capecitabine is contraindicated during pregnancy.

Breast-feeding
It is not known whether capecitabine is excreted in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. Breast-feeding should be discontinued while receiving treatment with capecitabine.

Fertility
There is no data on capecitabine and impact on fertility.

**Effects on ability to drive and use machines**

Capecitabine has minor or moderate influence on the ability to drive and use machines. Capecitabine may cause dizziness, fatigue and nausea.

**Undesirable effects**
The most commonly reported adverse drug reactions (ADRs) were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-

plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

Tabulated list of adverse reactions

ADRs related to the administration of capecitabine are listed in table 4 for capecitabine given as monotherapy and in table 5 for capecitabine given in combination with different chemotherapy regimens in multiple indications. The following headings are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

*Capecitabine Monotherapy:*

Table 4 Summary of related ADRs reported in patients treated with capecitabine monotherapy

| Body System | Very Common *All grades* | Common *All grades* | Uncommon *Severe and/or Life threatening (grade 3-4) or considered medically relevant* | Rare/Very Rare |
|---|---|---|---|---|
| *Infections and infestations* | | Herpes viral infection, Nasopharyngitis, Lower respiratory tract infection | Sepsis, Urinary tract infection, Cellulitis, Tonsillitis, Pharyngitis, Oral candidiasis, Influenza, Gastroenteritis, Fungal infection, Infection, Tooth abscess | |
| *Neoplasm benign, malignant and unspecified* | | | Lipoma | |
| *Blood and lymphatic system disorders* | | Neutropenia, Anaemia | Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia, Leukopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased/Prothrombin time prolonged | |
| *Immune system disorders* | | | Hypersensitivity | |
| *Metabolism and nutrition disorders* | Anorexia | Dehydration, Weight decreased | Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, Hypertriglyceridaemia, | |
| *Psychiatric disorders* | | Insomnia, Depression | Confusional state, Panic attack, Depressed mood, Libido decreased | |
| *Nervous system disorders* | | Headache, Lethargy Dizziness, Parasthesia Dysgeusia | Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorder, Neuropathy peripheral | Toxic leuko-encephalopathy (very rare) |
| *Eye disorders* | | Lacrimation increased, Conjunctivitis, Eye irritation | Visual acuity reduced, Diplopia | Lacrimal duct stenosis (rare), Corneal disorders (rare), keratitis |

| | | | | |
|---|---|---|---|---|
| | | | | (rare), punctate keratitis (rare) |
| *Ear and labyrinth disorders* | | | Vertigo, Ear pain | |
| *Cardiac disorders* | | | Angina unstable, Angina pectoris, Myocardial ischaemia/infarction, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations | Ventricular fibrillation (rare), QT prolongation (rare), Torsade de pointes (rare), Bradycardia (rare), Vasospasm (rare) |
| *Vascular disorders* | | Thrombophlebitis | Deep vein thrombosis, Hypertension, Petechiae, Hypotension, Hot flush, Peripheral coldness | |
| *Respiratory, thoracic and mediastinal disorders* | | Dyspnoea, Epistaxis, Cough, Rhinorrhoea | Pulmonary embolism, Pneumothorax, Haemoptysis, Asthma, Dyspnoea exertional | |
| *Gastrointestinal disorders* | Diarrhoea, Vomiting, Nausea, Stomatitis, Abdominal pain | Gastrointestinal haemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth | Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastrooesophageal reflux disease, Colitis, Blood in stool | |
| *Hepatobiliary disorders* | | Hyperbilirubinemia, Liver function test abnormalities | Jaundice | Hepatic failure (rare), Cholestatic hepatitis (rare) |
| *Skin and subcutaneous tissue disorders* | Palmar-plantar erythrodysaesthesia syndrome | Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyperpigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder | Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome | Cutaneous lupus erythematosus (rare), Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis (very rare) |
| *Muskuloskeletal and connective tissue disorders* | | Pain in extremity, Back pain, Arthralgia | Joint swelling, Bone pain, Facial pain, Musculoskeletal stiffness, Muscular weakness | |
| *Renal and urinary disorders* | | | Hydronephrosis, Urinary incontinence, Haematuria, Nocturia, Blood creatinine increased | |
| *Reproductive system and breast disorders* | | | Vaginal haemorrhage | |

| | | | | |
|---|---|---|---|---|
| *General disorders and administration site conditions* | Fatigue,<br>Asthenia | Pyrexia, Oedema peripheral, Malaise, Chest pain | Oedema, Chills, Influenza like illness, Rigors, Body temperature increased | |

*Capecitabine in combination therapy:*

Some of the ADRs are reactions commonly seen with the combination medicinal product (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin, hypertension seen with bevacizumab); however an exacerbation by capecitabine therapy cannot be excluded.

Table 5 Summary of related ADRs reported in patients treated with capecitabine in combination treatment in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to Capecitabine monotherapy

| Body System | Very common<br>*All grades* | Common<br>*All grades* | Rare/Very Rare |
|---|---|---|---|
| *Infections and infestations* | | Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection , Rhinitis, Influenza, Infection, Oral herpes | |
| *Blood and lymphatic system disorders* | Neutropenia, Leucopenia, Anaemia, Neutropenic fever, Thrombocytopenia | Bone marrow depression, Febrile Neutropenia | |
| *Immune system disorders* | | Hypersensitivity | |
| *Metabolism and nutrition disorders* | Appetite decreased | Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia | |
| *Psychiatric disorders* | | Sleep disorder, Anxiety | |
| *Nervous system disorders* | Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache | Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia | |
| *Eye disorders* | Lacrimation increased | Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred | |
| *Ear and labyrinth disorders* | | Tinnitus, Hypoacusis | |
| *Cardiac disorders* | | Atrial fibrillation, Cardiac ischaemia/infarction | |
| *Vascular disorders* | Lower limb oedema, Hypertension, Embolism and thrombosis | Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis | |

| | | | |
|---|---|---|---|
| *Respiratory, thoracic and mediastinal system disorders* | Sore throat, Dysaesthesia pharynx | Hiccups, Pharyngolaryngeal pain, Dysphonia | |
| *Gastrointestinal disorders* | Constipation, Dyspepsia | Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort | |
| *Hepatobiliary disorders* | | Hepatic function abnormal | |
| *Skin and subcutaneous tissue disorders* | Alopecia, Nail disorder | Hyperhidrosis, Rash erythematous, Urticaria, Night sweats | |
| *Musculoskeletal and connective tissue disorders* | Myalgia, Arthralgia, Pain in extremity | Pain in jaw , Muscle spasms, Trismus, Muscular weakness | |
| *Renal and urinary disorder* | | Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria | Acute renal failure secondary to dehydration (rare) |
| *General disorders and administration site conditions* | Pyrexia, Weakness, Lethargy, Temperature intolerance | Mucosal inflammation, Pain in limb, Pain, Chills, Chest pain, Influenzalike illness, Fever, Infusion related reaction, Injection site reaction, Infusion site pain, Injection site pain | |
| *Injury, poisoning and procedural complications* | | Contusion | |

Description of selected adverse reactions

*Hand-foot syndrome:*
For the capecitabine dose of 1250 mg/m$^2$ twice daily on days 1 to 14 every 3 weeks, a frequency of 53% to 60% of allgrades HFS may be observed in capecitabine monotherapy trials (comprising studies in adjuvant therapy in colon cancer, treatment of metastatic colorectal cancer, and treatment of breast cancer) and a frequency of 63% may be observed in the capecitabine/docetaxel arm for the treatment of metastatic breast cancer. For the capecitabine dose of 1000 mg/m$^2$ twice daily on days 1 to 14 every 3 weeks, a frequency of 22% to 30% of all-grade HFS may be observed in Capecitabine combination therapy.

*Diarrhoea:*
Capecitabine can induce the occurrence of diarrhoea, which may be observed in up to 50% of patients.

*Cardiotoxicity:*
In addition to the ADRs described in tables 4 and 5, the following ADRs with an incidence of less than 0.1% were associated with the use of capecitabine monotherapy: cardiomyopathy, cardiac failure, sudden death, and ventricular extrasystoles.

*Encephalopathy:*
Encephalopathy may also be associated with the use of capecitabine monotherapy.

Special populations
*Elderly patients:*
Patients ≥60 years of age treated with capecitabine monotherapy and an analysis of patients treated with capecitabine plus docetaxel combination therapy may show an increase in the incidence of treatment related grade 3 and 4 adverse reactions and treatment-related serious adverse reactions compared to patients <60 years of age. Patients ≥60 years of age treated with capecitabine plus docetaxel may also have more early withdrawals from treatment due to adverse reactions compared to patients <60 years of age.
Increasing age (by 10 year increments) may significantly be associated with an increased risk of developing HFS and diarrhoea and with a decreased risk of developing neutropenia.

*Gender*
Female gender may significantly be associated with an increased risk of developing HFS and diarrhoea and with a decreased risk of developing neutropenia.

*Patients with renal impairment:*
Patients treated with capecitabine monotherapy (colorectal cancer) with baseline renal impairment may show an increase in the incidence of treatment-related grade 3 and 4 adverse reactions compared to patients with normal renal function. Patients with moderately impaired renal function may show an increase in rate of dose reduction compared to patients with no or mild renal impairment and an increase in early withdrawals from treatment compared to patients with no or mild renal impairment.

**Overdose**

The manifestations of acute overdose include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic (antimetabolite), ATC code: L01BC06
Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.
There is evidence that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of

deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to create a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of DNA and RNA deprivation are most marked on those cells which proliferate more rapidly and which metabolise 5-FU at a more rapid rate.

**Pharmacokinetic properties**

Capecitabine dose reduction decreases systemic exposure to 5-FU more than dose-proportionally, due to non-linear pharmacokinetics for the active metabolite.

Absorption

After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-DFCR and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption, but only results in a minor effect on the AUC of 5'-DFUR, and on the AUC of the subsequent metabolite 5-FU.

*Distribution*

*In vitro* human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound, mainly to albumin.

Biotransformation

Capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumour tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations within tumour tissues. In the case of colorectal tumours, 5-FU generation appears to be in large part localised in tumour stromal cells. Following oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumour to plasma was 21.4 (ranged from 3.9 to 59.9, n=8) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 25.8, n=8). Thymidine phosphorylase activity as measured and found to be 4 times greater in primary colorectal tumour than in adjacent normal tissue. According to immunohistochemical studies, thymidine phosphorylase appears to be in large part localised in tumour stromal cells. 5-FU is further catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA).

Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of capecitabine

Elimination

The elimination half-life (t1/2 in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine unchanged

Combination therapy
No effect by capecitabine on the pharmacokinetics of docetaxel or paclitaxel (Cmax and AUC) and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR.
Pharmacokinetics in special populations

*Patients with hepatic impairment due to liver metastases:* In cancer patients with mild to moderate liver impairment due to liver metastases, the bioavailability of capecitabine and exposure to 5-FU may increase compared to patients with no liver impairment. There are no pharmacokinetic data on patients with severe hepatic impairment.

*Patients with renal impairment:* In cancer patients with mild to severe renal impairment, there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. Creatinine clearance may influence the systemic exposure to 5'-DFUR and to FBAL. FBAL is a metabolite without antiproliferative activity.
*Elderly:* Age has no influence on the pharmacokinetics of 5'-DFUR and 5-FU. The AUC of FBAL may increase with age (20% increase in age results in a 15% increase in the AUC of FBAL). This increase is likely due to a change in renal function.

## PHARMACEUTICAL PARTICULARS

### List of excipients

Anhydrous lactose, Croscarmellose sodium, Microcrystalline cellulose, Hypromellose, Purified water, Magnesium stearate, Talc, Titanium dioxide, Ferric oxide yellow, Ferric oxide red

### Incompatibilities

Not applicable

### Shelf life

Please refer outer package

### Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

### Nature and contents of container

Blister pack:
Capecitabine Tablets USP 150 mg and 500 mg: Blister of 10 tablets.

**MARKETING AUTHORISATION HOLDER**


Aurobindo Pharma Limited,
Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500 038,
Telangana, India.

**DATE OF PREPARATION OF THIS LEAFLET**

June 2018